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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/080,876	02/22/2002	Brian Robert Walker	674543-2001.6	2514

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EXAMINER	
KANTAMNENI, SHOBHA	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 06/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/080,876	WALKER ET AL.	
	Examiner	Art Unit	
	Shobha Kantamneni	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *NONE* is/are allowed.

6)☒ Claim(s) *14-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Finality of the previous Office action made on September 13, 2004 is hereby withdrawn, and new ground(s) of rejection are detailed below.

Claims 14-22 are pending and examined herein.

Claim Objections

Claim 22 is objected to because of the following informalities: Word "method" is missing in line 1, before the word "for" Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-15, 17, 19-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for carbenoxolone, **does not reasonably provide enablement for all inhibitors of reductase activity of 11 Beta HSD1 in general**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention **commensurate in scope** with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without **undue experimentation**. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404

where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

All of the rejected claims are drawn to an invention which pertains to a method of reducing circulating fatty acids by inhibiting reductase activity of 11-Beta-hydroxysteroid dehydrogenase 1(11-Beta HSD1) in adipose tissue in a patient, and method of treating insulin resistance or obesity by said inhibition. The nature of the invention is complex in that it encompasses a method of inhibiting reductase activity of 11-Beta HSD1 comprising administering to a patient **any** inhibitor of reductase activity of 11-Beta HSD1.

(2). Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass inhibiting reductase activity of 11-Beta HSD1 in adipose tissue in a patient by administering **any inhibitor** of reductase activity of 11-Beta HSD1 for treating insulin resistance or obesity.

(3). Guidance of the Specification / (4) Working Examples:

The specification provides general information as to the effect(s) of gluococorticoids on different body tissues. It also gives general information as to the effect of carbonoxolone on reductase activity of 11-Beta HSD1. The specification states that said inhibition of 11 Beta-reductase by carbenoxolone creates possibilities of novel medicament for treating deleterious effects of glucocorticoid excess.

The only working example with regards to the claimed inhibitors of reductase activity of 11-Beta HSD1 is the effect of carbenoxolone on insulin sensitivity.

(5). State of the Art:

While the state of the art is relatively high with regard to specific 11-Beta HSD1 reductase inhibitor the state of the art with regard to **any** reductase inhibitor of 11Beta-HSD1 for reducing circulating fatty acids and for treating obesity or insulin resistance in **general** is underdeveloped. Different inhibitors of reductase activity of 11-Beta HSD1 have different chemical structures and are expected to behave in different manners, evidence that the level of skill in this art is low relative to the difficulty of the task of determining a suitable inhibitor of reductase activity of 11-Beta HSD1 for the treatment of insulin resistance or obesity.

(6). Predictabilitv of the Art:

The invention is directed to a method of reducing circulating fatty acids by using **any** inhibitors of the reductase activity of 11-Beta HSD1 in general for the treatment of insulin resistance or obesity. It is well established that "the scope of

enablement various inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970).

It is further noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. Also one skilled in the art would recognize that it is highly unpredictable with regards to not only therapeutic effects, but also side effects, and especially serious toxicity due to drug accumulation or that may be generated by drug-drug interactions when and/or after administering to a host any agents represented by either an inhibitor of reductase activity of 11-Beta HSD1 and/or while the patient also administers other medicines. One of skill in the art would not be able to fully predict the possible treatment of insulin resistance or obesity herein and possible adverse effects occurring with many agents having the claimed functional properties. Thus, the instant claimed invention is highly unpredictable.

(7). The Quantity of Experimentation Necessary:

In order to practice the claimed invention, one of skill in the art would have to first envision a specific inhibitor of reductase activity of 11-Beta HSD1, a pharmaceutical carrier, a dosage for the inhibitor, the duration of treatment, route of treatment, etc. One of skill in the art would then need to test specific inhibitor of reductase activity of HSD1 in the model system to determine whether or not it is effective for reducing circulating fatty acids, and for treating insulin resistance or obesity and one would need to test for side effects and toxicity. If the treatment is unsuccessful, one of skill in the art would have to modify the first inhibitor of

reductase activity of 11-Beta HSD1, dosage, duration of treatment, route of administration, etc. Even if successful, however, one of skill in the art would then need to determine the magnitude of the side effects and toxicity of utilizing the inhibitor of reductase activity of 11-Beta HSD1. One of skill in the art would then need to determine whether or not the magnitude of the side effects could be reduced by increasing or decreasing the dosage of inhibitor of reductase activity of 11-Beta HSD1 while retaining the functional aspect. Once the functionality to toxicity ratio was maximized, one of skill in the art would need to determine whether or not the inhibitor of reductase activity of 11-Beta HSD1 which had been used was of sufficient benefit that it would serve as useful for treating insulin resistance or obesity. If not, one would need to select another inhibitor of reductase activity of 11-Beta HSD1 and repeat the process until a sufficient benefit to detriment ratio had been achieved.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

The instant claims encompass **any and all** compounds broadly that would inhibit the reductase activity of 11 Beta HSDI. The present specification lacks a structural description and/or description of other compounds encompassed by the claimed invention and, thus, does not enable the skilled artisan to make and use the claimed invention commensurate in scope with these claims.

Further, these recitations may broadly encompass those known and **unknown** compounds having the recited functions as of the instant filing date, as discussed above. Note those **future known** compounds yet to be discovered and/or made. Hence, those unknown or future known compounds encompassed by claims herein must require to additional or future research to discover, establish or verify their usefulness. Therefore, as indicated above the skilled artisan has to exercise **undue experimentation** to practice the instant invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-15, 17, 19-22 are rejected under 35 U.S.C. 112, second paragraph, as failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention,

Claims 14-15, 17, 19-22 are drawn to methods of reducing circulating fatty acids by inhibiting reductase activity of 11-Beta HSD1 by administering a compound or a composition which inhibits reductase activity of 11-Beta-HSDI, and a method of treating obesity or insulin resistance. The present specification discloses carbenoxolone as the only exemplified compound encompassed by the instant invention and lacks a structural description and/or description of other compounds encompassed by the claimed invention. Therefore, the ordinary

artisan in the art would be unable to determine other compounds encompassed by the claimed invention and, thus, the metes and bound of the instant claims.

Claims 14, 21 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: The claim omits any active agent employed in inhibiting the reductase activity of 11-Beta HSD1 is inhibited.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Stewart et al.

Stewart et al. disclose an enzyme complex 11 Beta-hydroxysteroid dehydrogenase (11β-OHSD), which consists of 11 Beta-dehydrogenase which converts cortisol to cortisone and 11 Beta-reductase i.e 11-Beta HSD1 which converts cortisone to cortisol. Stewart et al. further discloses that when carbenoxolone is administered, it inhibits 11-Beta-reductase activity of 11-Beta HSD1, thus reduces cortisol production. It is also disclosed that carbenoxolone is

used in the treatment of peptic ulceration (see page 501, Abstract; page 506, col. 2, lines 4-27). Thus Stewart anticipates the instant claims 14-20.

Claims 14-20 are rejected under 35 U.S.C 102(b) as being anticipated by Walker et al.

Walker et al. disclose that the enzyme 11 β-hydroxysteroid dehydrogenase (11-Beta-OHSD) catalyzes two activities: the 11 β-dehydrogenase conversion of cortisol to inactive cortisone and the reverse 11 β-reductase conversion of cortisone to cortisol. See page 221, col. 2, 2nd paragraph, lines 4-8. Walker further discloses that carbenoxolone inhibits both 11 β-reductase and 11 β-dehydrogenase acitivities in man. It is also reported that the inhibition of 11 β-dehydrogenase and 11 β-reductase activities by carbenoxolone varies between organs, such that 11 β-dehydrogenase is predominant in the kidney and 11 β-reductase predominant in liver. Inhibition of both enzymes results in increased intra-renal cortisol concentration but decreased intra-hepatic cortisol concentration. See page 224, col. 2, para 2, lines 15-26. Thus Walker anticipates the instant claims 14-20.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker et al. in view of Goodman and Gilman, pages 1463-1473.

The instant claims are drawn to a method of treating obesity, insulin resistance by regulating reductase activity of 11-Beta HSD1 in a patient comprising administering to said patient an inhibitor of said reductase activity of 11-Beta HSD1.

Walker et al. is as discussed above.

Inparticular, Walker et al. teaches that inhibition of 11 β-dehydrogenase and 11 β-reductase activities by carbenoxolone varies between organs, such that 11 β-dehydrogenase is predominant in the kidney and 11 β-reductase predominant in liver. Inhibition of both enzymes results in increased intra-renal cortisol concentration but decreased intra-hepatic cortisol concentration.

Walker et al. does not expressly teach the treatment of obesity or insulin resistance by administering carbenoxolone.

Goodman and Gilman teaches that corticosteroids have numerous actions in the body, including induction of gluconeogenesis in the liver and inhibition of glucose utilization in the peripheral tissue such as adipose tissue and skin. See Goodman and Gilman, pages 1463-1473, especially page 1467, col. 2, lines 16-41.

From the teachings of Walker et al. and Goodman that it would have been obvious to a person of ordinary skill in the art at the time of invention to treat insulin resistance by inhibiting reductase acitivity of 11-Beta HSD1 because

inhibition of reductase activity of 11-Beta HSD1 results in decrease in hepatic cortisol concentration.

One of ordinary skill in the art at the time of invention would have been motivated to administer carbenoxolone with the expectation of decreasing the cortisol concentration, and thus decreasing gluconeogenesis, which is promoted by cortisol in the liver, which induces a number of enzymes involved in gluconeogenesis and amino acid metabolism. Also one of ordinary skill in the art at the time of invention would have been motivated to administer carbenoxolone with the expectation of enhancing the glucose utilization in the adipose tissue, which is inhibited by cortisol, and thus increasing the insulin sensitivity.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 14-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim

15 of copending Application No. 10/061,044. Although the conflicting claims are not identical they are not patentably distinct from each other because the subject matter embraced in the instant claims overlaps with the stated claims of '044. It would have been obvious to a person of ordinary skill in the art at the time of invention to administer carbenoxolone disclosed in '044 for reducing circulating fatty acids by reductase activity of 11-Beta HSD1 with the expectation of reducing intracellular glucocorticoid concentration, and thus reducing circulating levels of fatty acids.

This is a provisional obviousness-type double patenting rejection.

Claims 14-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-17 of copending Application No. 10/080,875. Although the conflicting claims are not identical they are not patentably distinct from each other because the compounds used in the method of inhibiting reductase activity of 11-Beta HSD1 in a patient are same. It would have been obvious to a person of ordinary skill in the art at the time of invention to administer carbenoxolone disclosed in '875 with the expectation of reducing circulating fatty acids by reductase activity of 11-Beta HSD1 in adipose tissue in a patient.

This is a provisional obviousness-type double patenting rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone

number is 571-272-2930. The examiner can normally be reached on Monday-Friday, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Shobha Kantamneni
Patent Examiner
Art Unit 1671

5/31/05
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